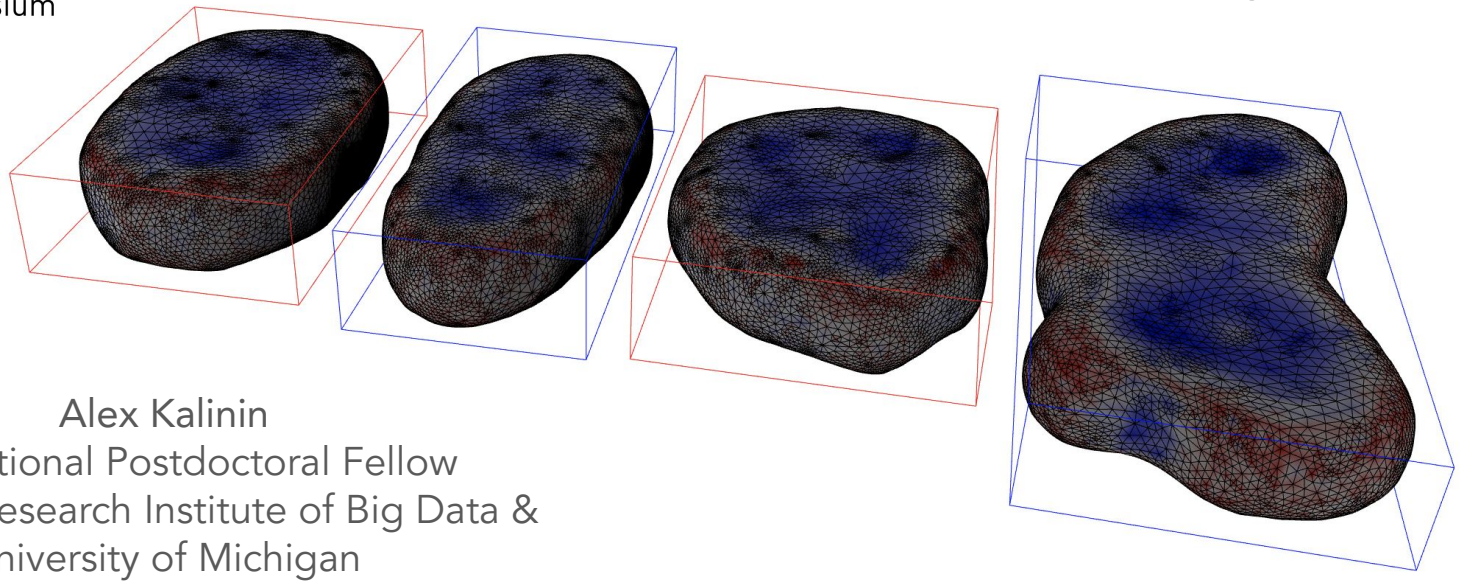
深圳市大数据研究院
Shenzhen Research Institute of Big Data

UNIVERSITY OF MICHIGAN

Crick **BioImage Analysis** Symposium

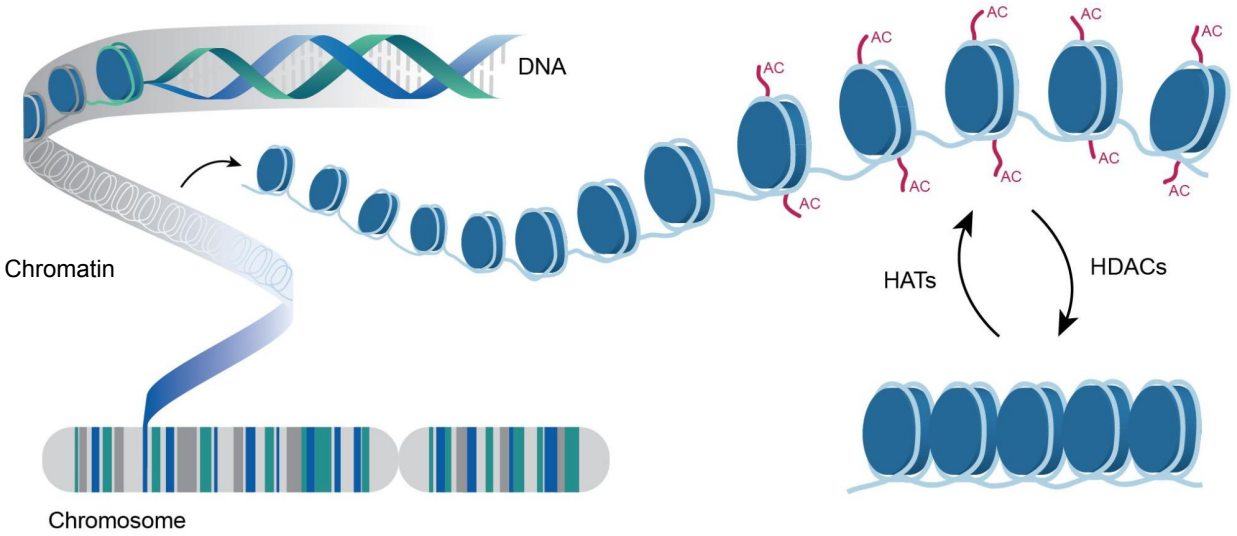
Shape modeling for 4D nuclear morphology analysis in VPA-treated astrocyte cells



Alex Kalinin
International Postdoctoral Fellow
Shenzhen Research Institute of Big Data &
University of Michigan

CBIAS 2021, November 23

Chromatin structure governs the genomic function



euchromatin (open)

increased access to DNA

transcriptional activation

heterochromatin (closed)

restricted access to DNA

transcriptional repression

HATs—histone acetyltransferases HDACs—histone deacetylases

HDAC inhibitors shifts the balance toward greater histone acetylation, DNA exposure, and chromatin decondensation.

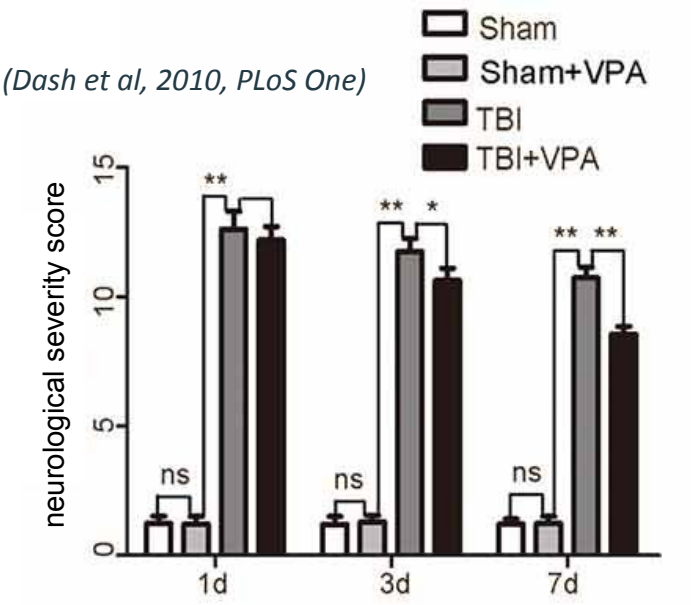
(Phimmachanh et al., 2020, Front. Cell Dev. Biol.)

Valproic acid (VPA) remodels chromatin

VPA is a histone deacetylase (HDAC) inhibitor that induces chromatin decondensation.

Facilitates recovery in traumatic brain injury in animal models (rats, swine).

(Dash et al, 2010, PLoS One)



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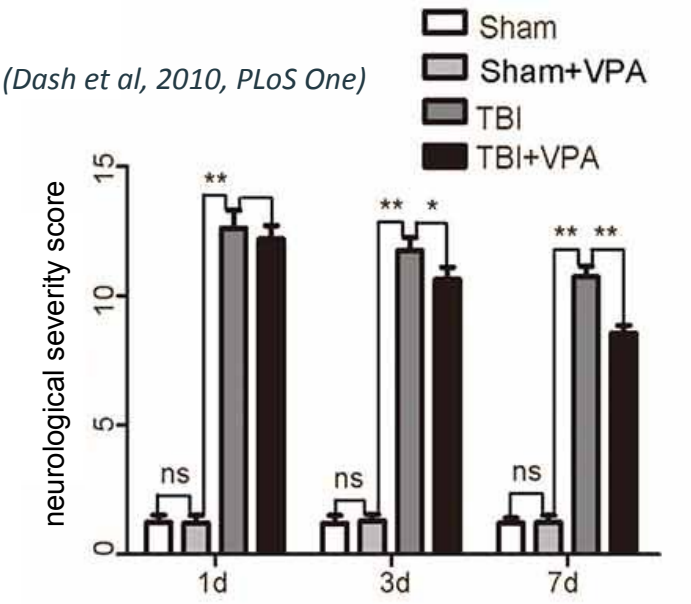
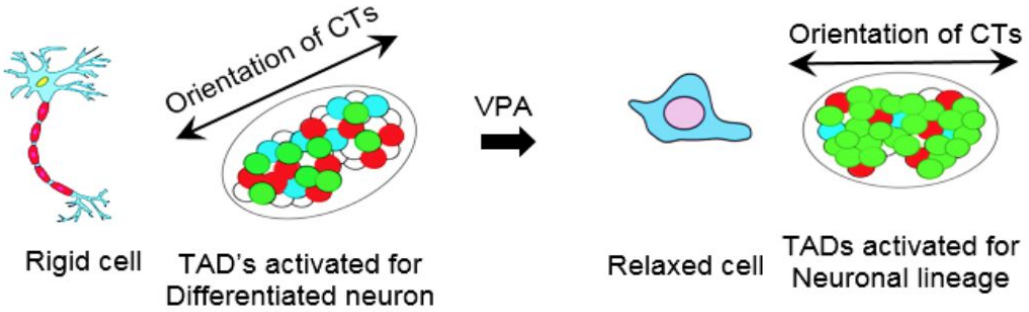


VPA is used to potentiate cells for reprogramming by chromatin decondensation.



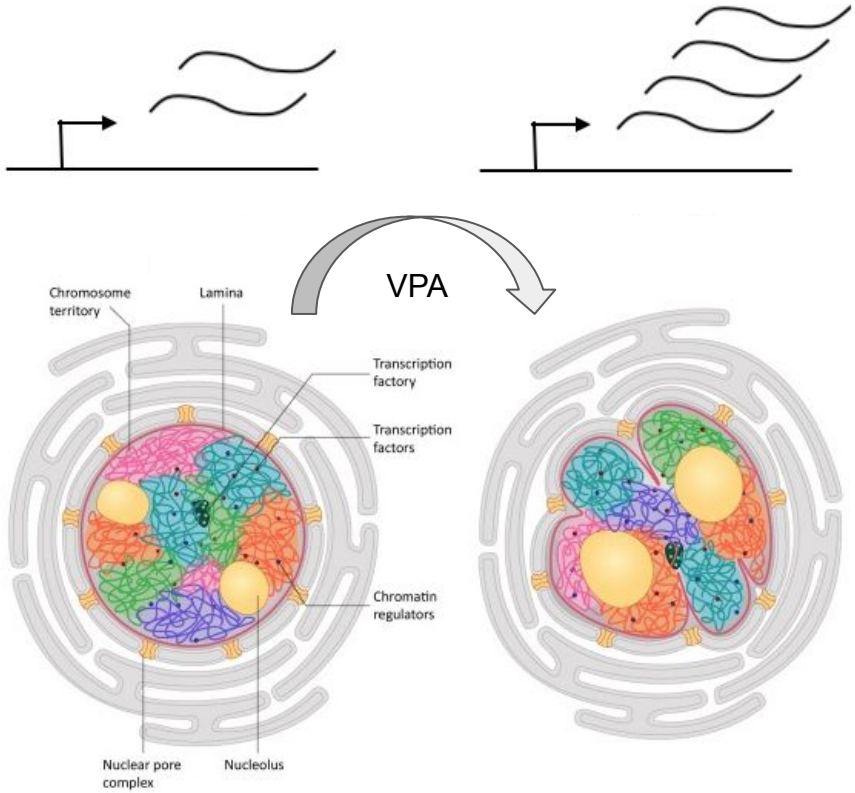
(Higgins et al, 2018, Pharmacogenomics)

Chromatin is a key regulator of nuclear shape

Changes in chromatin state are reflected in nuclear morphology.

An opportunity to connect a molecular mechanism with an effect on mesoscale:

- modulate chromatin states
- measure nuclear size and shape changes

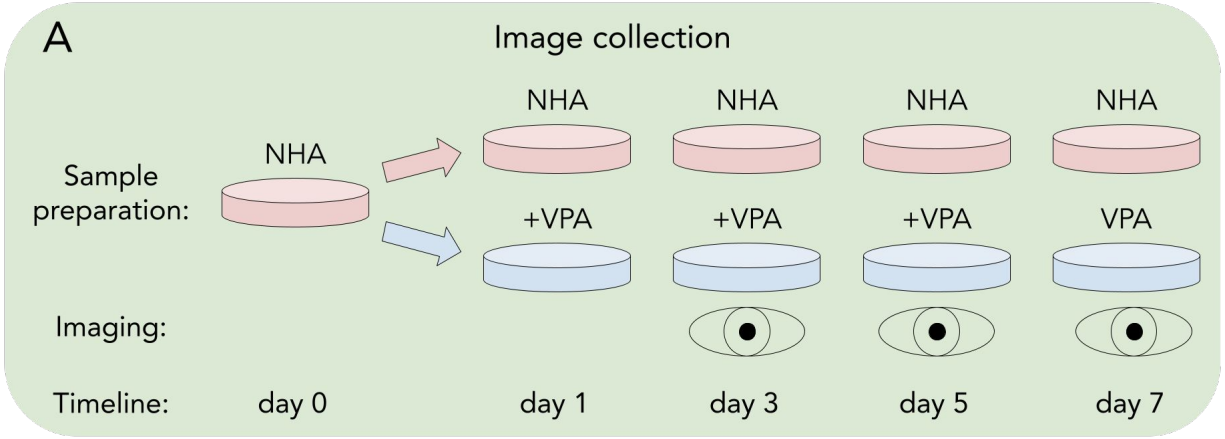


(Uhler and Shivashankar, 2018, Trends in Cancer)

How VPA-induced chromatin remodeling affects nuclear morphology over time?

Normal human astrocyte (NHA) cells:

- treated with 1.5 mM of VPA on days 1, 3, and 5
- stained with DAPI and imaged in 3D confocal on days 3, 5, and 7

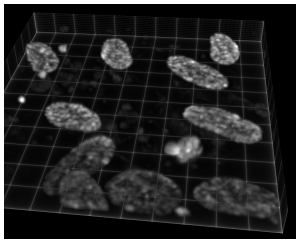


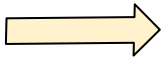
~100 segmented nuclei per condition

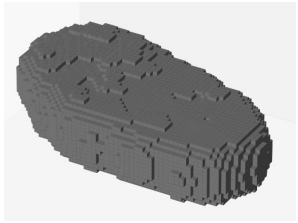
(Kalinin et al, 2021, Molecular Biology of the Cell)

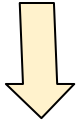
Feature extraction: voxels

segmentation









principal axes
volume
bounding box
convex hull
extent
solidity

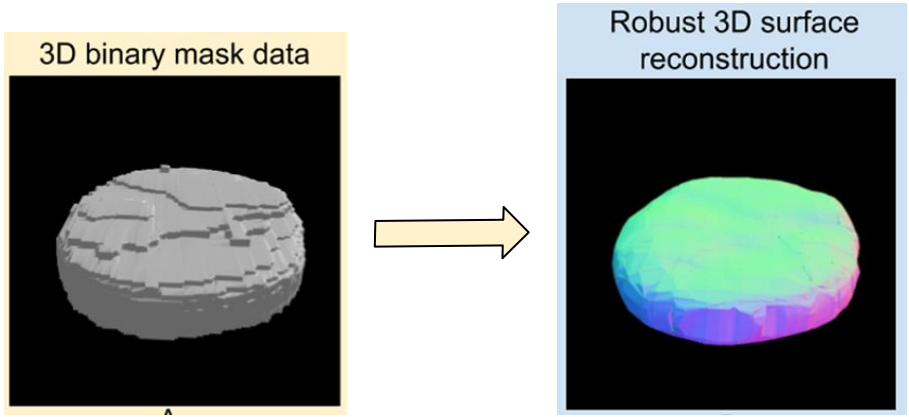
extracting size and shape measures

(Kalinin et al, 2018, CVPRW'18)

Feature extraction: from voxels to surface

Surface extraction and refinement with Laplace-Beltrami eigen-projection algorithm (generalization of spherical harmonics to an arbitrary manifold)

Extracts smooth surface
(removes segmentation artifacts)



(Shi et al, 2010, IEEE Trans Med Imaging)

(Kalinin et al, 2018, Scientific Reports)

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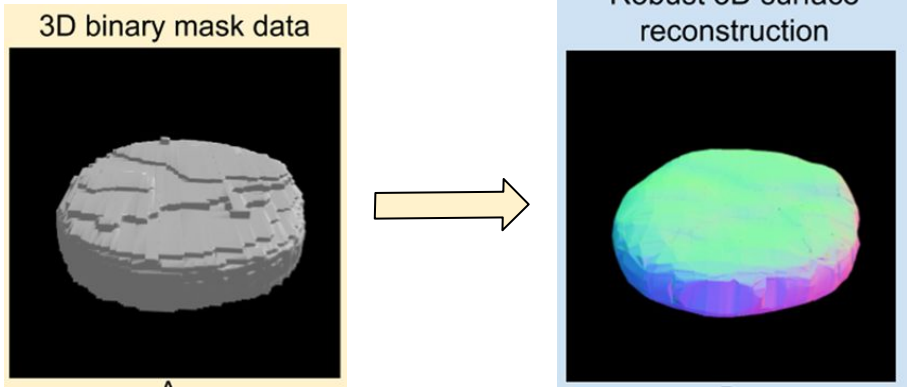
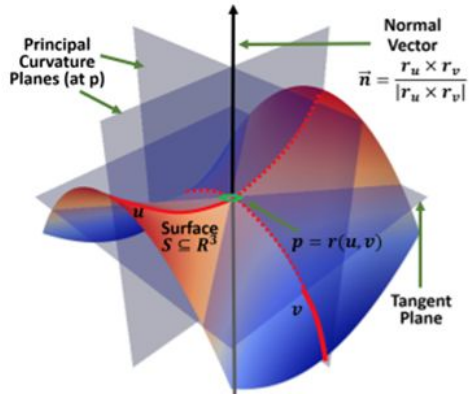


(Shi et al, 2010, IEEE Trans Med Imaging)

Enables surface-based feature extraction
(curvatures, curvedness, shape index, etc)

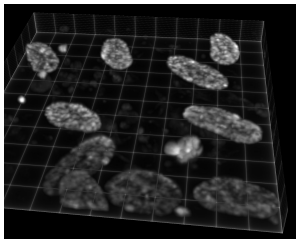


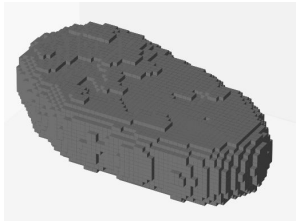
(Kalinin et al, 2018, Scientific Reports)

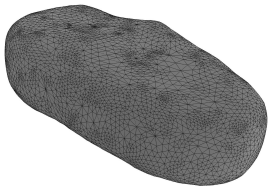
Feature extraction: voxels

segmentation

surface extraction







extracting size and shape measures

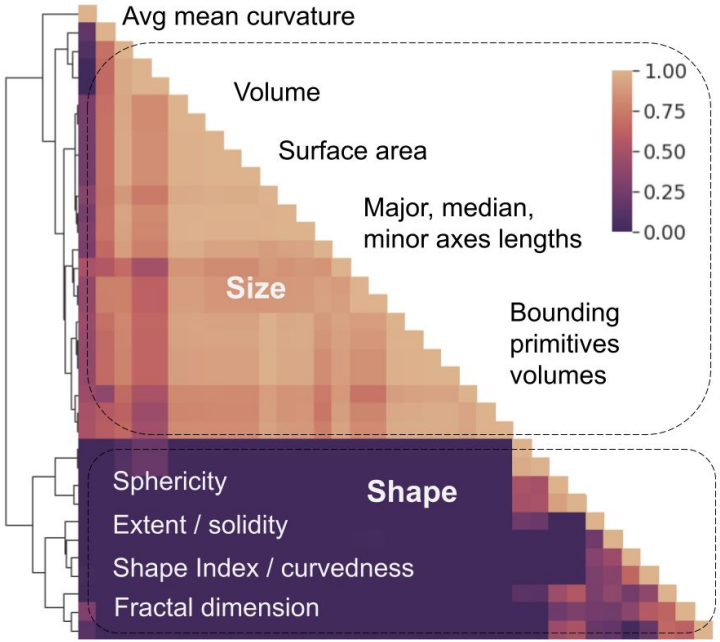
principal axes
volume
bounding box
convex hull
extent
solidity

principal axes
volume
bounding box
convex hull
extent
solidity

mean curvature
Gaussian curvature
curvedness
shape index
fractal dimension

Feature selection

Selected top-7 features to reduce redundancy and aid interpretability



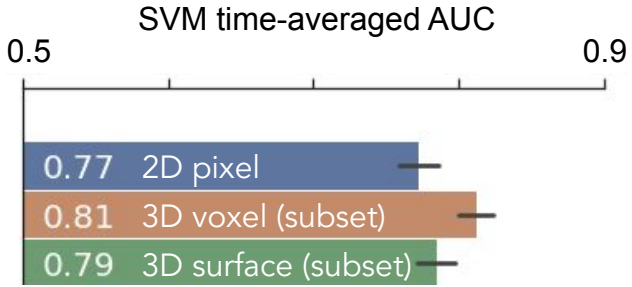
surface-based:
- median axis length
- convex hull volume
- bounding sphere volume
- average mean curvature
- sphericity
- shape index

voxel-based:
- solidity

(Kalinin et al, 2021, Molecular Biology of the Cell)

Feature set classification performance analysis

We compared different (sub-)sets of features for NHA vs VPA classification



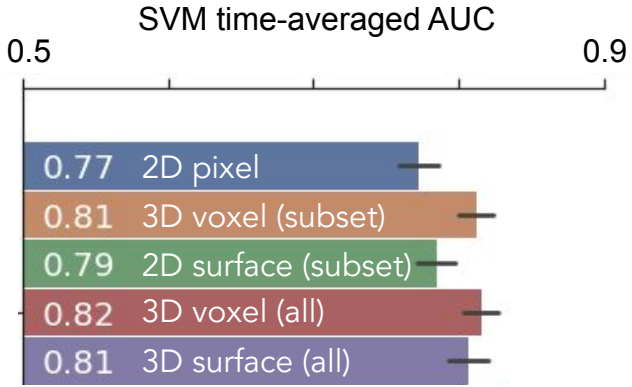
2D vs 3D

- 2D performed slightly worse than any 3D set

Similar results for other classifiers (log reg, random forest, etc.)

Feature set classification performance analysis

We compared different (sub-)sets of features for NHA vs VPA classification



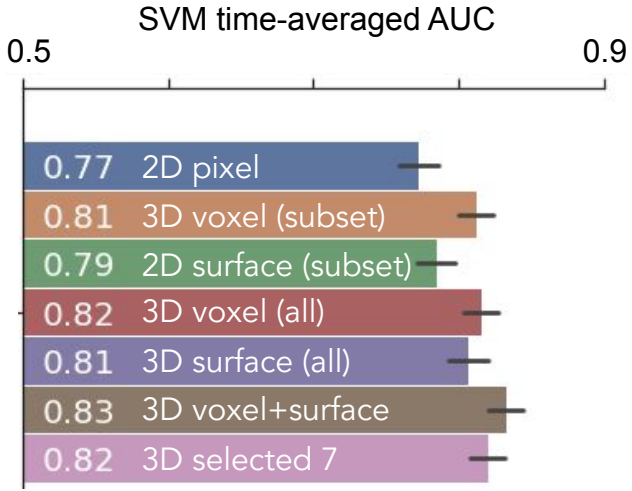
Voxel vs surface

- 2D performed slightly worse than any 3D set
- 3D voxel slightly better than surface
  on a common subset and on full feature set

Similar results for other classifiers (log reg, random forest, etc.)

Feature set classification performance analysis

We compared different (sub-)sets of features for NHA vs VPA classification



All vs selected

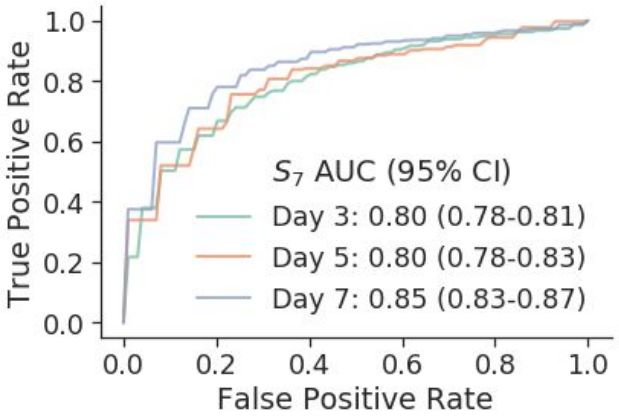
- 2D performed slightly worse than any 3D set
- 3D voxel slightly better than surface
  on a common subset and on full feature set
- best results when combining all features together
- selected 7 features (6 surface+1 voxel) is 2nd best

Similar results for other classifiers (log reg, random forest, etc.)

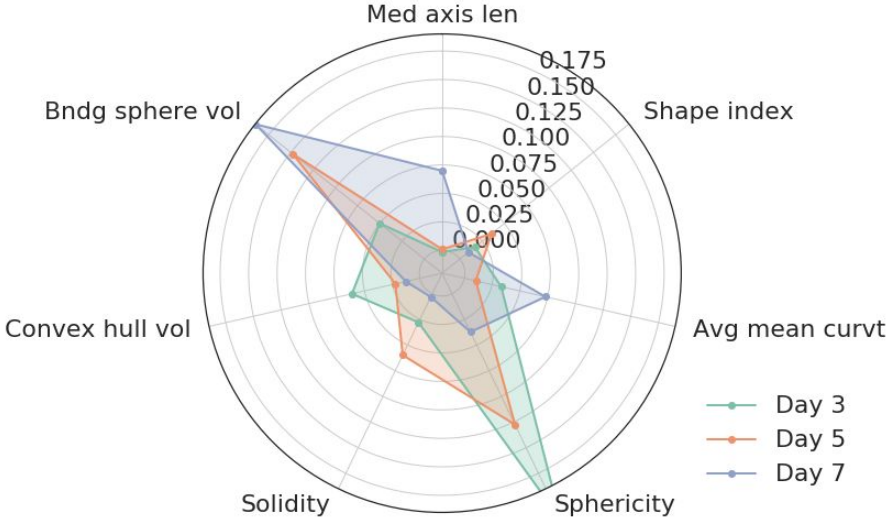
Classification performance analysis

7 selected features (6 surface-based and 1 voxel based)

Better discrimination by the last day:
- 80% AUC for days 3 and 5
- 85% AUC for day 7

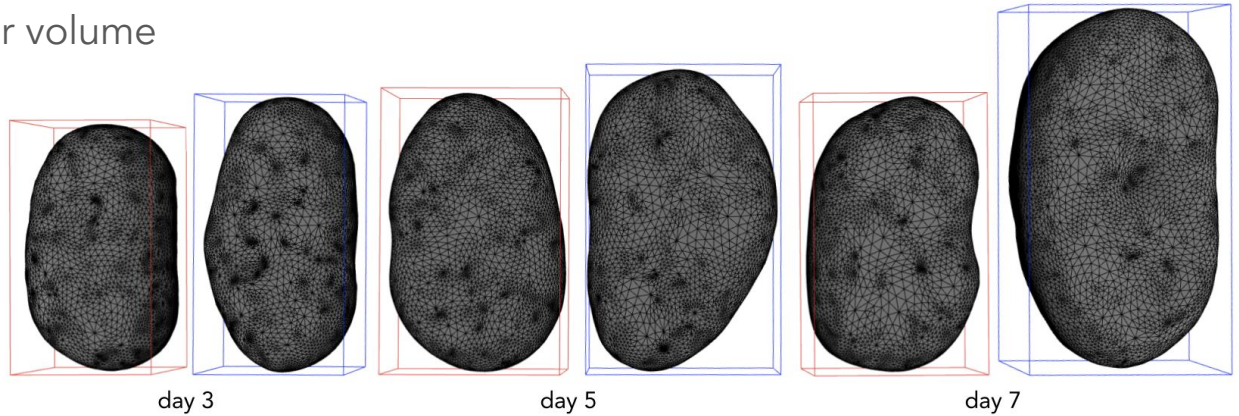


Different features were most important for different timepoints

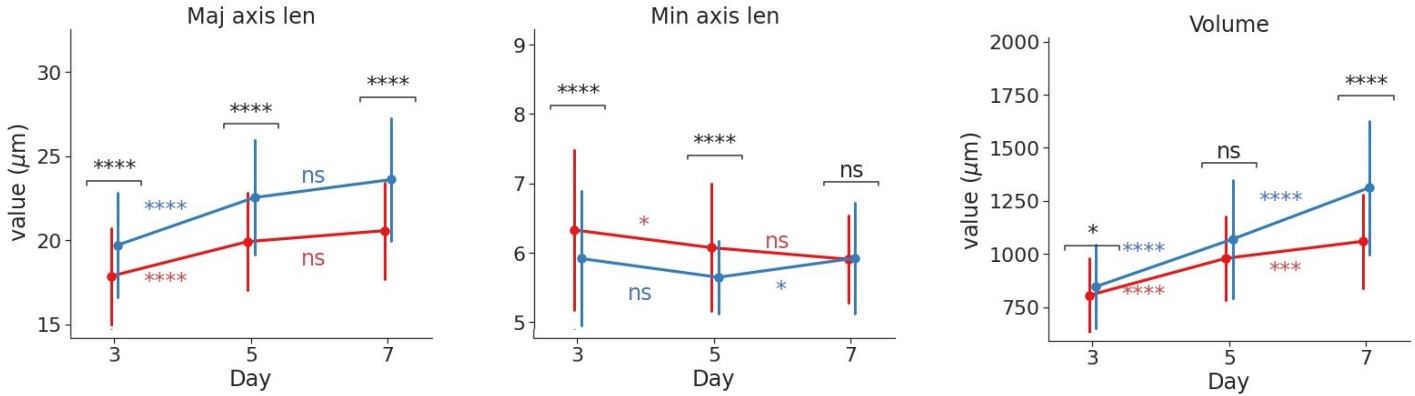


VPA induced increased nuclear size

- longer major axis and shorter minor axis (elongation and flattening)
- increasingly larger volume

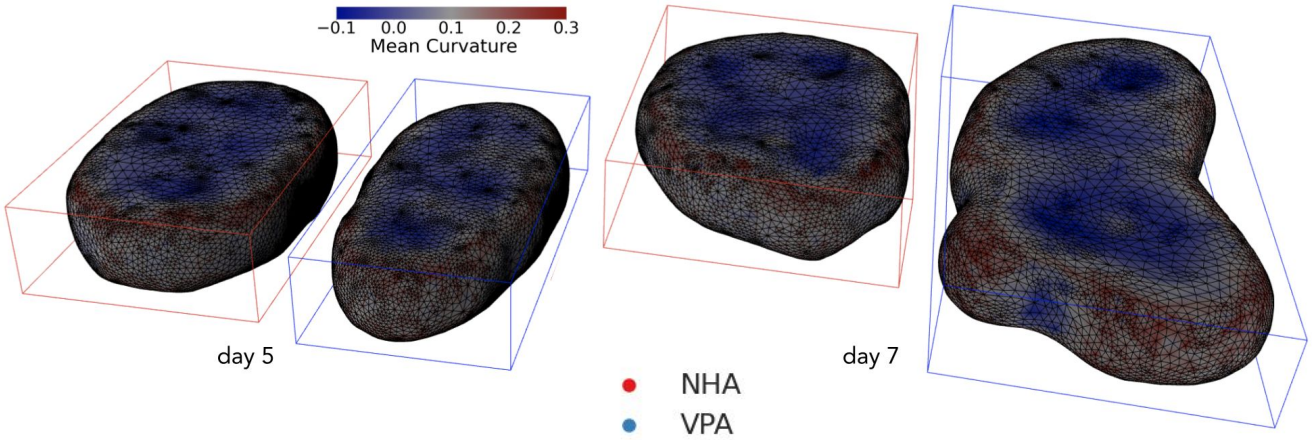


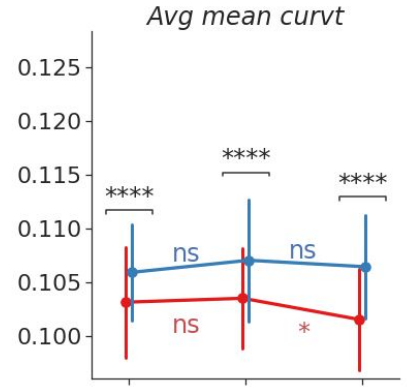
NHA
VPA

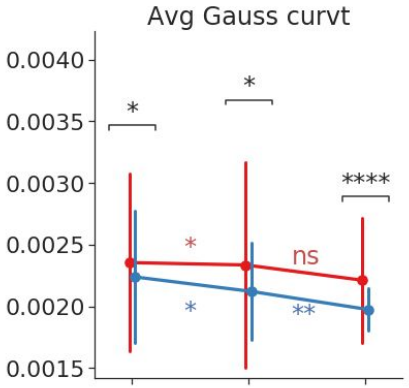


VPA induced nuclear shape irregularity

- lower sphericity (also due to flattening and elongation)
- higher mean curvature (more convex & less concave points)
- higher shape irregularity by day 7 per other measures







Conclusions

- VPA induces chromatin reorganization manifested in nuclear morphology changes
- 4D morphometry allows accurate & interpretable characterization of nuclear form
- both 3D voxel and surface measures are informative
- shape modeling can be applied to other components
- results can be correlated with data from other assays, such as Hi-C, to study how altered functional properties are correlated with morphology

Thank you!

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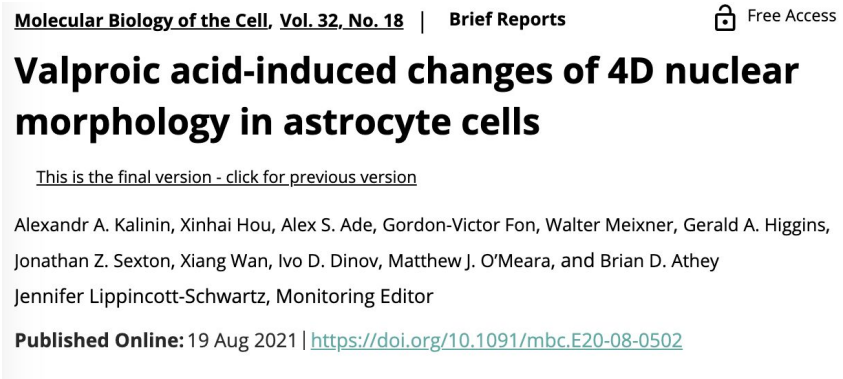

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Valproic acid-induced changes of 4D nuclear morphology in astrocyte cells

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